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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,772	06/25/1999	WILLEM JAN MARIE VAN DE VEN	702-990278	1485

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EXAMINER

KIM, YOUNG J

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/242,772

Applicant(s)

VAN DE VEN ET AL.

Examiner

Young J. Kim

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 53 is/are allowed.
- 6) ☒ Claim(s) 54 and 55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The present Office Action is responsive to the Amendment received on October 3, 2005.

Preliminary Remark

Claims 1-52 and 56-58 have been canceled.

Claims 53-55 are pending and are under prosecution.

Applicants have not disputed Examiner's claim interpretation with respect to claim 53 (page 3 of the previous Office Action).

Therefore, the scope of claim 53 is limited to an isolated nucleic acid sequence consisting of SEQ ID NO: 116, as SEQ ID NO: 116 consists of 7313 base pairs (see page 32 of the paper Sequence Listing).

Claim Interpretation

The phrase, "base pairs *corresponding to* exon 1 of CTNNB1" is interpreted to mean "base pairs of exon 1 of CTNNB1." For clarity, Applicants are suggested to use the latter phrase.

Specification

The objection to the specification for containing an active hyperlink, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005, removing the active hyperlink.

The objection to the specification for containing description requiring clarification made in the Office Action mailed on June 29, 2005 (page 4 of the Office Action), is withdrawn in view of the Amendment received on October 3, 2005, amending the specification so as to clarify the issue.

Claim Rejections - 35 USC § 112

The rejection of claims 55-57 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005, canceling claims 56 and 57, and amending claim 55 to clarity.

The New Matter rejection of claim 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005, canceling the claim.

The New Matter rejection of claims 54 and 55 under 35 U.S.C. 112, first paragraph (made in pages 9-10 of the office action), as failing to comply with the written description requirement, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005, amending the claims.

The New Matter rejection of claims 54 and 55 under 35 U.S.C. 112, first paragraph (made in page 8 of the office action), as failing to comply with the written description requirement, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005, amending the claims.

The scope of enablement rejection of claims 54 and 55 under 35 U.S.C. 112, first paragraph, made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005.

Rejections – New Grounds, Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

Claim 54 depends from claim 53. claim 55 depends from claim 53.

Claim 53 is drawn to an isolated nucleic acid consisting of SEQ ID NO: 116. According to the instant specification, SEQ ID NO: 116 is PLAG1 which consists of exons 1, 2, 3, 4, and 5.

Claim 54 is drawn to an isolated hybrid nucleic acid sequence consisting of the nucleic acid of claim 53 fused to a CTNNB1 translocation partner of PLAG1, wherein said isolated hybrid nucleic acid sequence contains 509 base pairs corresponding to exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1.

Claim 54, **as amended** embraces an isolated hybrid nucleic acid consisting of PLAG1 having fused thereto 509 base pairs of exon 1 of CTNNB1, wherein the fusion occurs to exons 3 to 5. The deletion of the word, "fragment," from claim 54 results in the change of claimed hybrid nucleic acid, further resulting in new matter as discussed fully below.

Structurally, the hybrid nucleic acid of claim 54 would have the below structure (Structure I):

Exon 1 – Exon 2 – 509 bp of CTNNB1 – Exon 3 – Exon 4 – Exon 5

The specification provides for the description for a hybrid nucleic acid consisting of the below structure:

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509 bp of exon 1 of CTNNB1 – Exon 3 – Exon 4 – Exon 5 (Structure II; *see also* structure A of Figure 6B)

The application as originally filed does not contemplate the hybrid nucleic acid of structure I, and hence, the amendment introduces new matter.

Claim 55 is drawn to an isolated hybrid nucleic acid sequence consisting of the nucleic acid of claim 53 fused to CTNNB1, wherein said isolated hybrid nucleic acid sequence contains 614 base pairs corresponding to exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1.

The claim, *as amended*, embraces an isolated hybrid nucleic acid consisting of PLAG1 having fused thereto 614 base pairs of exon 1 of CTNNB1, wherein the fusion occurs to exons 2 to 5. The change in the dependency of claim 55 (from claim 54 to claim 53) results in the change of claimed hybrid nucleic acid, further resulting in new matter as discussed fully below

Structurally, the hybrid nucleic acid of claim 55 would have the below structure (Structure III):

Exon 1 – 614 bp of exon 1 of CTNNB1 – Exon 2 – Exon 3 – Exon 4 – Exon 5.

The specification provides for the description of a hybrid nucleic acid consisting of the below structure:

614 bp of CTNNB1 – Exon 2 – Exon 3 – Exon 4 – Exon 5 (Structure IV; *see also* structure B of Figure 6B, page 53, lines 1-8; page 44, lines 1-9).

The application as originally filed does not contemplate the hybrid nucleic acid of structure III, and hence, the amendment introduces new matter.

Deletion of new matter is required.

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Claims 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in *In Re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

Nature of the Invention & Breadth of the claims:

The nature of the invention relates to hybrid nucleic acid molecules (or fusion nucleic acid) resulting from translocation of genes, in the instant case, hybrid nucleic acid molecules produced from translocation of PLAG1 and CTNNB1 (see page 2, lines 37-38; page 6, lines 15-20; page 35, lines 3-6), wherein said hybrid nucleic acid molecules are implicated with cancer (pleomorphic adenoma; page 42, lines 9-38; page 43, line 15 through page 44, line 10).

While the specification discloses specific hybrid nucleic acid molecules produced as a result of translocation process (*see* page 43-44), wherein said hybrid nucleic acid molecules are implicated with cancer, the claimed hybrid nucleic acid molecules (claims 54 and 55) are not enabled under the “use” criteria of the “make and use” requirement under enablement.

The structure embraced by the claimed hybrid nucleic acid of claims 54 and 55 are reproduced below:

Claim 54:

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Exon 1 – Exon 2 – 509 bp of CTNNB1 – Exon 3 – Exon 4 – Exon 5 (Structure I)

Claim 55:

Exon 1 – 614 bp of exon 1 of CTNNB1 – Exon 2 – Exon 3 – Exon 4 – Exon 5 (Structure II)

Amount of direction or guidance & Working Examples:

The instant specification discloses specific guidance with respect to the hybrid nucleic acid molecules produced from translocation of PLAG1 and CTNNB1. Particularly, the instant specification discloses that in “seven out of seven t(3;8) tumors analyzed (Figure 6), the hybrid nucleic acid molecules were present (page 43, lines 34-37). In tumors CG368, CG588, CG682, CG752, and T9587, PCR products of 509 base pairs and 614 base pairs were generated, whereas in tumors CG644 and CG753, only the PCR product of 509 base pairs was found. The specification states that PCR product of 509 base pair corresponds to a hybrid transcript containing exon 1 of CTNNB1 and exons 3-5 of PLAG1 (page 44, lines 3-5). The PCR product of 614 containing an extra 15 base pairs corresponds to the alternatively spliced exon 2 of PLAG1, wherein it points toward the presence of a related isoform consisting of exon 1 of CTNNB1 and exons 2 to 5 of PLAG1 (page 44, lines 5-9). The specification discloses that this fact was “confirmed by nucleotide sequence analysis of the PCR products.” (page 44, lines 9-10)

The specification discloses two hybrid nucleic acid molecules in Figure 6B, wherein Structure A exhibits the hybrid nucleic acid molecule comprising 509 base pairs of CTNNB1 and Structure B exhibits the hybrid nucleic acid molecule comprising of the 614 base pairs of CTNNB1.

Clearly, the figure indicates that the hybrid nucleic acid molecule of Structure A only consists of 519 base pair of exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1; and the hybrid nucleic acid

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molecule of Structure B only consists of 614 base pair of exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1.

This is further evidenced by the instant specification wherein on page 45, beginning at line 8, states that transcripts produced by tumors did not have exon 1 of PLAG1 because “exon 1-specific probe failed to hybridize to this transcript (page 45, lines 8-11).

The instant specification has no guidance or working examples with respect to the hybrid nucleic acid molecules claimed by claims 54 and 55.

State of Prior art & Skill level of the artisan:

The skill level of the artisan in question is deemed high and the state of prior art with respect to identifying hybrid nucleic acid molecules are determined to be routine.

Unpredictability of the art:

While the identification of a hybrid nucleic acid molecule is routine, it remains highly unpredictable whether a particular hybrid nucleic acid molecule would be implicated with cancer, requiring empirical determination.

Quantity of Experimentation:

One of skill in the art would first look to the instant specification for guidance in determining whether a hybrid nucleic acid molecules of claims 54 and 55 would be implicated with cancer. Neither the specification nor the prior art would reasonably guide said skilled artisan so as to use the claimed hybrid nucleic acid molecules as cancer marker without undue experimentation as such hybrid molecule would not appear to exist in nature, clearly evidenced by lack of guidance/working examples from the instant specification and from the prior art.

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The rejection of claims 54 and 55 under 35 U.S.C. 102(b) as being anticipated by Nollet et al. (Genomics, March 1996, vol. 32, pages 413-424) as evidenced by Takayama et al. (American Journal of Pathology, 1996, vol. 1, pages 39-46), made in the Office Action mailed on June 29, 2005 is withdrawn in view of the Amendment received on October 3, 2005.

Conclusion

Claim 53 is free of prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

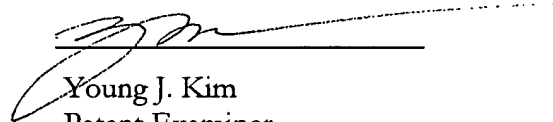
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also

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be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.


Young J. Kim
Patent Examiner
Art Unit 1637
12/27/2005

**YOUNG J. KIM
PATENT EXAMINER**

yjk